

Guidance to NIH Investigators Related to Protocols Involving Products from the Aseptic Unit of the CC Pharmaceutical Development Section

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1. Who to Contact at NIH

If after reading this document, you have additional questions, please contact the PDS Task Force co-chairs, Larry Tabak (Lawrence.Tabak@nih.gov) and Kathy Hudson (Kathy.Hudson@nih.gov). Please cc: Carrie Wolinetz, NIH Associate Director for Science Policy (carrie.wolinetz@nih.gov), on all correspondence.

2. Which PDS Products are Affected

Operation of the PDS aseptic manufacturing component was suspended on May 22, 2015. All protocols that use products prepared in the PDS using aseptic techniques for administration to research participants, including cell and gene therapy preparations handled in PDS, have been affected by the suspension of those operations. FDA is in the process of reviewing all protocols involving sterile PDS products, including cell/gene therapy products, whether or not they are under an IND, BB-IND, or IDE (hereafter, referred to as IND), and whether or not an alternative source has been found for the product.

If you have not yet been notified that your protocol involves a product affected by the suspension, please check the current compilation of affected protocols that will be available under “Quick Links” on the Clinical Center’s Intranet site (<http://intranet.cc.nih.gov/index.html>) by COB 6-24-2015. If you do not see your protocol on the list, but know or think your protocol involves an aseptic PDS-prepared product, you must contact David Henderson (DHenderson@cc.nih.gov) immediately.

3. Process for Finding Alternative Sources for PDS Products and What You Have to Do Before Using Them

John Gallin’s team is working to identify alternative sources for PDS products. To find out whether an alternative source has been identified, please contact Dr. Gallin (JGallin@cc.nih.gov).

Even if an alternative source is available, you must follow the process outlined below in #7 to request approval before proceeding with your protocol.

4. Who to Contact at FDA If You are the IND Holder with a Protocol Involving a PDS Product

If you are the PI on a protocol involving a PDS product and you are the IND holder, you should contact the FDA project manager who oversees your study with any questions about PDS products. You will need to cite the IND number, which is in your IND file, as is the contact information for the appropriate FDA project manager. If you are unable to reach the FDA project manager, you should contact the FDA Division that oversees the medical product/therapeutic area and ask to speak to the Chief Project Manager. The central telephone number for those divisions is available through this link to FDA’s Enhanced Communication team: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327281.htm>.

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If it is still not clear who at FDA should be contacted, please email all of the following individuals at FDA: Sandy Kweder (Sandra.Kweder@fda.hhs.gov) (CDER), Beth Duvall (Elizabeth.Duvall@fda.hhs.gov) (CDER), Peter Marks (Peter.Marks@fda.hhs.gov) (CBER), and Joe Franklin (Joseph.Franklin@fda.hhs.gov) (OC).

5. What to Do If You Are Not the IND Holder of a PDS-Product Protocol Under IND

If you are the PI of a protocol that uses an IND product, but you are not the IND holder, you should contact the holder as soon as possible to inform them of the situation and to ensure that they comply with required reporting. Inform the IND holder which product(s) in your protocol is affected and that they need to contact FDA immediately. Tell the sponsor which products in your protocol are affected.

As the PI, whether or not you are the IND holder, you are responsible for completing an unanticipated problem report to the IRB explaining that the suspension is affecting the availability of your study material. The process for reporting, along with suggested language for the report, is provided in #12 below. You are responsible for working with Dr. Gallin's team to identify alternative sources. You are responsible for working with the IND holder to obtain FDA permission to use an alternative source or to obtain an exemption in order to use an existing PDS product.

6. Affected IND Holders – How to Submit a Safety Report to the FDA

For each IND that is currently associated with an active protocol (whether or not participants have enrolled or had drug administered yet) or any protocol that has enrolled participants since June 1, 2013, you must submit an [IND safety report](#) to the FDA project manager who oversees your study and, if you haven't taken this step yet, please do so **IMMEDIATELY**. (See Appendix A below for excerpts and links to FDA regulatory text and guidance on safety reporting requirements. The safety report should be sent to the FDA project manager assigned to the IND (see #4 above). Please cc: Carrie Wolinetz, NIH Office of Science Policy (OSP) (carrie.wolinetz@nih.gov), and Margaret Sanders, NIH Office of Human Research Protections (OHSRP) (margaret.sanders@nih.gov).

- The following suggested language may be used in the FDA safety report:

“Operations of the sterile production component of the Pharmaceutical Development Section (PDS) at the NIH Clinical Center were suspended on May 22, 2015. Between May 19 and May 29, 2015, the FDA conducted an inspection of the PDS and issued a report on May 29 (<http://www.nih.gov/news/health/jun2015/nih-04.htm>). The report noted deficiencies in the physical facility, including flaws in the air handling system, and operational failures including inadequate quality control, insufficient employee training, and lack of compliance with standard operating procedures. These observations could impact the safety of research subjects. I received a notification on 5/31/2015 that production of sterile materials in the PDS was suspended, including the product(s) _____ used in this protocol.”

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- Please also include the following language in the safety report so that the FDA may communicate with NIH leadership about your IND and protocol.

“I authorize FDA to communicate directly with the NIH Task Force on the PDS chaired by Drs. Larry Tabak and Kathy Hudson regarding this IND.” This will enable NIH and FDA to coordinate on all protocols affected by the PDS

- If other investigators are participating in your protocol and they are also receiving PDS products, provide a copy of the safety report to them.

If you believe that you may not need to file a safety report, contact your FDA project manager immediately. Please cc Carrie Wolinetz in the NIH Office of Science Policy (OSP) (carrie.wolinetz@nih.gov) and Margaret Sanders in the NIH Office of Human Research Protections (OHSRP) (margaret.sanders@nih.gov) on the email and be sure to forward FDA's response to them. If you have any questions, please contact Dr. Wolinetz (carrie.wolinetz@nih.gov).

7. Procedure for Seeking Exemptions to Administer PDS Products to Participants

For products under an IND, the exemption process is being handled by the FDA. For products not under IND, the exemption process is being handled by NIH with advice from FDA. Investigators should follow these steps. Approval of the NIH IRB is also required.

IND Studies:

1. If the health and well-being of a participant will be adversely affected by discontinuing the treatment, contact the FDA project manager (see #4 above) who will work with the IND holder to resolve questions about administration of the investigational product.
2. If the FDA project manager approves the use of the product (the approval must be documented in email), notify the Chair of the IRB for the study and follow the process in #8 below to seek IRB approval to use the produce and to amend the consent document and process.
3. Seek consent from participant(s) in the study to accept this additional risk.
4. Notify David Henderson (DHenderson@cc.nih.gov) and Carrie Wolinetz (carrie.wolinetz@nih.gov) by e-mail that all approvals have been obtained.
5. Dr. Henderson will notify the Pharmacy or the Cell Processing Service to release the product.

Studies that Are Not Under IND:

1. If the health and well-being of a participant will be adversely affected by discontinuing the treatment, contact the following at FDA to request assistance in assessing the risk/benefit analysis for the use of the product:
 - a. For cell therapy, gene therapy, biologics: Peter Marks at FDA/CBER (240-507-4942, Peter.Marks@fda.hhs.gov).

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- b. For drug products: Sandy Kweder (Sandra.Kweder@fda.hhs.gov) (CDER), Beth Duvall (Elizabeth.Duvall@fda.hhs.gov) (CDER).
 - c. If you are unsure, please email all three FDA contacts.
2. The FDA contacts will consult with appropriate colleagues at FDA to conduct the risk/benefit assessment.
3. Once FDA contacts respond in writing, send FDA's assessment to Jim Anderson (james.anderson2@nih.gov) in the NIH Office of the Director, with cc to Dr. Wolinetz (carrie.wolinetz@nih.gov) and Dr. Henderson (DHenderson@cc.nih.gov).
4. Dr. Anderson will make the final decision about whether or not to move forward with the use of the product(s) and will notify you and Drs. Wolinetz and Henderson of his decision.
5. If Dr. Anderson approves the exemption, notify the Chair of the IRB for the study and follow the process in #8 below to seek IRB approval to use the product and to amend the consent document and process.
6. Once IRB approval has been granted notify Dr. Henderson (DHenderson@cc.nih.gov).
7. Seek consent from participant(s) in the study to accept this additional risk.
8. Dr. Henderson will notify the Pharmacy or Cell Processing Service to release the product.

8. Obtaining IRB Approval to Proceed and to Amend the Informed Consent Process

1. Create a protocol amendment to request IRB approval to use the product and an addendum to the consent document to explain the PDS issue and the risk assessment conducted by FDA or NIH (Dr. Anderson). See Suggested Language for the Informed Consent Addendum below for suggested wording for the addendum.
2. Submit the proposed amendment to the IRB via an amendment action along with a copy of the FDA or NIH (Dr. Anderson) approval to use the potentially affected PDS product.
3. The IRB Chair must decide whether to approve this language as an expedited action per 45 CFR 46.110 (b) 2 and 21 CFR 56.110(b)(2) as "minor changes in previously approved research during the period (of one year or less) for which approval is authorized." The Chair should also state whether he/she concurs with the risk assessment. If the Chair agrees with the risk assessment, and that this is a minor change, the Chair may approve the addendum and affirm the appropriateness of the exemption on an expedited basis. The Chair should review and note whether the FDA or NIH approval for use of the product applies to the entire protocol or to specific participants, and IRB approval must be consistent with the FDA or NIH approval. If the IRB Chair does not agree with the risk assessment or thinks that the change is not minor, the full IRB must be convened to review the addendum and the request to proceed with the research.
4. After IRB approval, the Office of Protocol Services (<http://intranet.cc.nih.gov/ops/index.html>) will process the amendment and post the amended consent document.
5. After review and discussion of the information with the research participant, the participant should be asked to sign the addendum indicating that they understand and voluntarily agree to continue study participation. Whoever obtains the participant's consent and witnesses his/her signature should also sign the addendum.
6. The signed consent form will be filed in the research file/medical records and a copy provided to the participant.

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9. Suggested Language for the Informed Consent Addendum

For Studies Under an IND That Received an FDA Exemption:

“This addendum provides new information about this study, <insert name of study>, in which you are enrolled. The information in the consent you signed previously is unchanged.

The NIH Clinical Center Pharmaceutical Development Service (PDS) helps make the <study drug name> used in this study. PDS operations were recently suspended by NIH leadership after some contaminated material was discovered while it was being prepared for another study. The PDS is undergoing a full review and changes are being made to make sure that processes are in place to prevent anything like this from happening again. Until then, PDS study products cannot be given to participants unless the Food and Drug Administration (FDA) has approved an exemption, after considering on a case-by-case basis, whether another source of the product is available, the participant has a critical need for the study drug, and a careful risk-benefit analysis has been done to determine whether the risk of discontinuing the study drug is greater than the risk of receiving a PDS product.

[Include A for PDS Aseptic Products]

- A. <Lay description of the specific exemption request to FDA.> After weighing these considerations, the FDA has determined that your risk in receiving the <study drug name> is extremely low, and they are allowing it to be administered to you.”

[Include B for PDS Cell/Gene Therapy Products]

- B. The PDS product helps preserve the cells used in this protocol, but the product it uses for that purpose is not actually given to you. Also, the cells used in this protocol have to pass many tests or they can't be given to you. After weighing these considerations, the FDA has determined that your risk in receiving these cells is extremely low, and they are allowing it to be administered to you.”

For Studies Not Under IND That Received an Exemption from NIH Leadership:

“This addendum provides new information about this study, <insert name of study>, in which you are enrolled. The information in the consent you signed previously is unchanged.

The NIH Clinical Center Pharmaceutical Development Service (PDS) helps to make the <study drug name> used in this study. PDS operations were recently suspended by NIH leadership after some contaminated material was discovered while it was being prepared for another study. The PDS is undergoing a full review and changes are being made to make sure that processes are in place to prevent anything like this from happening again. Until then, PDS study products cannot be given to participants unless NIH leadership has approved an exemption, after considering on a case-by-case basis, whether another source of the product is available, the participant has a critical need for the study drug, and a careful risk-benefit analysis has been done including with input from the Food and Drug Administration, to determine, whether the risk of discontinuing the study drug is greater than the risk of receiving a PDS product.

[Include A for PDS Aseptic Products]

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- A. <Lay description of the specific exemption request.> After weighing these considerations, the NIH leadership has determined that your risk in receiving the <study drug name> is extremely low, and they are allowing it to be administered to you.”

[Include B for PDS Cell/Gene Therapy Products]

- B. The PDS helps preserve the cells used in this protocol, but the product it uses for that purpose is not actually given to you. Also, the cells used in this protocol have to pass many tests or they can't be given to you. After weighing these considerations, the NIH determined that your risk in receiving these cells is extremely low, and they are allowing it to be administered to you.”

10. Communicating with Participants

Since the suspension of operations of the aseptic PDS unit, all participants who have received or who were being prepared to receive a sterile product have been notified about the problem and, as necessary, informed about the need for monitoring. If you have participants who received or are scheduled to receive PDS sterile products but who have not been notified, please contact Carrie Wolinetz (carrie.wolinetz@nih.gov) immediately.

A group of infectious disease experts, led by PDS Task Force member, Dr. Steven Holland, is currently conducting a risk assessment to determine whether further participant notification is warranted. Once the risk assessment is completed, you will be notified if additional actions are needed. If you have any questions in the meantime, please contact Carrie Wolinetz (carrie.wolinetz@nih.gov).

11. Addressing Participant Complaints

If you receive a complaint from one of your participants, please follow the guidance in NIH Human Research Protection Program (HRPP)'s [SOP 22 Research Subject Information and Services and Research-Related Complaints from Research Subjects](#).

1. The office/person receiving the complaint should document subject's name, address, phone number, protocol number, PI name, date of incident, and an explanation of the concern or complaint.
2. If the complaint cannot be resolved by the office/person who receives the complaint, matters involving human subjects issues should be referred to the IRB Chair and the OHSRP (Dr. Lynnette Nieman, Director, OHSRP at niemanl@mail.nih.gov and to Charlotte Holden, Deputy Director, OHSRP at holdenc@od.nih.gov).
3. The IRB and OHSRP will review the complaint and determine whether further action is needed.

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12. Notifying the IRB: Reporting Unanticipated Problems

HRPP's [SOP 16 Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations](#) requires that serious unanticipated problems (UPs) be reported to the IRB within seven days of PI notification of an event. Please use your IRB Problem Report Form.

1. All active protocols list at posted on the Clinical Center's Intranet site (<http://intranet.cc.nih.gov/index.html>) that administered a PDS sterile product to participants must file a UP report. This applies to all protocols, including the cell and gene transfer protocols, regardless of whether they are under an IND. If you have not yet filed a UP report with your IRB and with OHSRP (ohsr_nih_ddir@od.nih.gov), please do so immediately. If you have questions, contact OHSRP.
 - a. In addition, the UP may include: (1) discontinuation of a protocol medication, creating an increased risk to your subjects; or (2) continuation of protocol medication under an approved exemption (see information above on the process for seeking exemptions), with an increased risk to subjects because of possible contamination.
 - b. Please use the following narrative in your UP report, identify the number of affected subjects and describe other issues specific to your protocol, including the proposed plan for these subjects.

“Operations of the sterile production component of the Pharmaceutical Development Section (PDS) at the NIH Clinical Center were suspended on May 22, 2015. Between May 19 and May 29, 2015, the FDA conducted an inspection of the PDS and issued a report on May 29 (<http://www.nih.gov/news/health/jun2015/nih-04.htm>). The report noted deficiencies in the physical facility, including flaws in the air handling system, and operational failures including inadequate quality control, insufficient employee training, and lack of compliance with standard operating procedures. These observations could impact the safety of research subjects. I received a notification on 5/31/2015 that production of sterile materials in the PDS was suspended, including the product _____ used in this protocol.”

2. OHSRP reports UPs to both the FDA (for IND, BB-IND and IDE protocols) and OHRP.
3. You should provide an update to the IRB if the mitigation plan changes.

13. Reporting NIH Administrative Holds and FDA Clinical Holds to the IRB

HRPP's [SOP 11 Suspensions and Terminations of IRB Approval and Administrative](#) requires investigators to report to their IRB if their protocol has been put on administrative hold. All PDS aseptic protocols are effectively on administrative hold unless an exemption is sought and approved. No further reporting to the IRB is necessary in this regard. If FDA places a clinical hold on the protocol, you must notify your IRB within five days.

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14. IRB Review/Approval on a Per Protocol or Per Subject Basis

For protocols under IND that have been granted an exemption to allow use of a PDS product, FDA has advised that the IRB may approve the continuation of the study on either a per protocol basis or a per subject basis. The NIH Task Force recommends a consistent approach be taken by the IRBs and that the approval be granted on a protocol basis for protocols under IND and protocols not under an IND unless there is safety or ethical concern that would warrant a subject by subject consideration. FDA will inform the NIH when IRB approval of protocols should be granted on a subject by subject basis.

15. Future Protocols Anticipating PDS Product Manufacturing

The PDS sterile production unit will be closed for the foreseeable future while assessments are being made regarding remediation. The timeline for resuming PDS aseptic operations is not clear at this time. Therefore, PIs preparing or submitting new protocols should anticipate using another facility to produce relevant research related products. For more information on alternative production facilities, please contact Dr. Gallin (JGallin@cc.nih.gov).

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Appendix A

Relevant FDA Regulatory and Guidance References

Excerpt of FDA's IND Regulations on Safety Reporting [21 CFR 312.32](#)

312.32(c)(1) *IND Safety Reports*. The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

312.32 (c)(1)(i) *Serious and unexpected suspected adverse reaction*. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- (A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- (B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- (C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

312.32 (c)(1)(ii) *Findings from other studies*. The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

312.32 (c)(1)(iii) *Findings from animal or in vitro testing*. The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-

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related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

(c)(1)(iv) *Increased rate of occurrence of serious suspected adverse reactions.* The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

312.32 (c)(1)(v) *Submission of IND Safety Reports.* The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a FDA Form 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

Excerpt of FDA's IND Regulations on Assurance of IRB Review [21 CFR 312.66](#)

An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Excerpt of FDA's IND Regulations on Sponsor Responsibilities [21 CFR 312.50](#)

General responsibilities of sponsors. Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

Excerpt from [FDA Guidance on Safety Reporting Requirements for INDs and BA/BE Studies](#) (page 13)

The sponsor must also report expeditiously any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug (21 CFR 312.32(c)(1)(ii) and (iii)). These reports are required for studies from any source, regardless of whether they are conducted under the IND or by the sponsor (21 CFR 312.32(c)(1)(ii) and (iii)). A finding that suggests a *significant risk* would ordinarily result in a safety-related change in the protocol,

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informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation. For example, actions often taken in response to a significant risk finding include immediate revision of the informed consent, intensification of subject monitoring, revised eligibility criteria or screening procedures, enrollment hold, or consideration of discontinuation of the trial. The sponsor is also required to submit protocol amendments that describe changes to the protocol or other documents (21 CFR 312.30(b)) in addition to the IND safety report.

Excerpt from [FDA Guidance on Adverse Event Reporting to IRBs Guidance – Improving Human Subject Protection](#) (page 2)

Sponsors are specifically required to notify all participating investigators (and FDA) in a written IND Safety Report of “any adverse experience associated with the use of the drug that is both serious and unexpected” and “any finding from tests in laboratory animals that suggests a significant risk for human subjects” (21 CFR 312.32(c)(1)(i)(A),(B)). And, more generally, sponsors are required to “keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use” (21 CFR 312.55(b)).

FDA Regulatory and Guidance Links

FDA IND Safety Reporting Regulations 21 CFR 312.32

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=312.32>

FDA IND Regulations General responsibilities of sponsors 21 CFR 312.50

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=312.50>

FDA Guidance on Safety Reporting Requirements for INDs and BA/BE Studies

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm227351.pdf>

FDA Guidance on Adverse Event Reporting to IRBs Guidance – Improving Human Subject Protection

<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126572.pdf>